REMARKS

I. Status of the Claims

Claims 7, 9-13, 21, 30-32, 34 and 35 were pending in the application. Upon entry of this amendment, claims 7, 9, 11-13, 30-32, 34 and 35 are pending. Claims 7, 13, 30, and 34 have been amended. Claims 8, 14-20, 22-29, and 33 were previously cancelled. Claims 10 and 21 have been cancelled herein.

In order to expedite prosecution, claims 7 and 30 have been amended to recite that the claimed methods are directed to assessing the risk that a test sample contains a cancerous breast, colon or prostate cell or that a human patient has breast, colon, or prostate cancer. Support for these amendments can be found, for example, in the specification of US2005/0227917 in Example 105, paragraphs [0160], [0161], [0179], [0337], [0340], [0343], [0346], [0348], [0350], [0352], [0536], [0540], [0544], [0548], [0551], [0553], [0557], [0560], [0631] and [0632].

Claim 13 has been amended to correct antecedent basis issues.

Claim 34 has been amended to be consistent with amended claim 30.

As there are no issues of new matter with respect to the amended claims, entry of the amendments is respectfully requested.

Cancellation and amendment of the claims is made without prejudice, without intent to abandon any originally claimed subject matter, and without intent to acquiesce in any rejection of record. Applicants request reconsideration of the pending claims in view of the following remarks

II. Rejection under 35 U.S.C. 112, first paragraph, written description

Claims 7, 9, 11-13, 21, 30-32, and 34 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. Specifically, the Office alleges that there is a lack of written description for the terms "full complement" and "complement".

Since claims 7, 30 and 34 have been amended to exclude the terms "full complement" and "complement", Applicants respectfully assert that the rejections are now moot and request that the rejections of claims 7, 9, 11-13, 21, 30-32 under 35 U.S.C. 112 be withdrawn.

III. Rejection under 35 U.S.C. 112, first paragraph, enablement

Claims 7, 9, 11-13, 21, 30-32, and 34 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The Office alleges that the subject matter was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention without undue experimentation.

To the extent the rejection is applicable to the currently amended claims, Applicants respectfully traverse the rejection and its supporting remarks. In light of the currently amended claims, the specification provides more than adequate support to enable one of skill in the art to make and use the claimed invention commensurate in scope with the claimed invention. The Examiner has asserted that undue experimentation would be required; however, as indicated in *In re Wands*, undue experimentation is evaluated based upon eight factors: quantity of experimentation, the amount of direction or guidance provided, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claims. Undue experimentation is not required for one of skill in the art to make and use the presently claimed invention. This is made clear by application of each of the *Wands* factors.

Nature of the Invention

The first *Wands* factor cited by the Office is the nature of the invention. In this case, making and using the invention requires only routine molecular biology techniques and is a matter of routine testing of breast, colon or prostate samples for expression of SEQ ID NO: 23702. For claim 7 and its dependents, it would involve routine testing of cells for a gene product comprising SEQ ID NO: 23702. Similarly, for claim 30 and its dependents, it would involve routine testing of

tissue samples from patients for the level of nucleic acid comprising a nucleotide sequence at least 95% identical to SEQ ID NO: 23702.

The Breadth of the Claims

The second *Wands* factor cited by the Office is the breadth of the claims. The Office states that claims are broadly drawn to methods of detecting and diagnosing cancer based solely on the over-expression of SEQ ID NO: 23702.

With the present amendment, claim 7 has been amended to recite that the methods are directed to assessing the risk of a human breast, colon or prostate cell being cancerous by detecting over-expression of SEQ ID NO: 23702 rather than detecting and diagnosing cancer by detecting over-expression of SEQ ID NO: 23702. Claim 7 has also been amended to remove the "full complement" and "complements" language, which further limits the breadth of the claims.

Claim 30 has been similarly amended to reflect that the methods are directed to assessing the risk of a human patient having breast, colon or prostate cancer by detecting over-expression of SEQ ID NO: 23702. Again, removal of the "full complement" and "complements" language further limits the breadth of the claims.

Therefore, the breadth of the claims is not unduly broad, particularly given the amendment of the claims to clarify the use of the methods.

Guidance in the Specification and Working Examples

The third and fourth *Wands* factors cited by the Office are the amount of direction or guidance provided and the presence of working examples. The Office alleges that the specification does not teach detection of cancerous cells based solely on the expression of SEQ ID NO: 23702 nor does it teach diagnosing any type of cancer based solely on the expression level of SEQ ID NO: 23702.

In view of the amendments to the claims, Applicants assert that the specification provides more than adequate guidance for the presently pending claims. The amended claims relate to

assessment of risk of cancer by detection of over-expression of SEQ ID NO: 23702. Several working examples in the specification disclose the use of differentially expressed genes as a risk assessment tool to be used in combination with other methods for evaluating the cancer phenotype of a sample, for example, see paragraph [337], which states "The differential expression of these polynucleotides can be used as a diagnostic marker, a prognostic marker, for risk assessment, patient treatment and the like. These polynucleotide sequences can also be used in combination with other known molecular and/or biochemical markers." Further, the data in Example 105 demonstrate that SEQ ID NO: 23702 is significantly over-expressed in breast, colon and prostate cancer cells in a percentage of human patients. Example 105 was a controlled experiment where both healthy and cancerous cells were obtained from the same patient to directly compare gene expression profiles of the two samples in order to distinguish which genes were significantly over-expressed in the cancerous cells. Over-expression of a gene in a cancerous cell may be correlated with its cancerous phenotype. Example 105 shows that SEQ ID NO: 23702 is overexpressed in cancerous cells and therefore indicates that the gene expression profile of SEQ ID NO: 23702 is a useful biomarker to be considered when assessing the risk of a breast, colon or prostate cell being cancerous.

The Office questions the fact that the specification only teaches detection of cancerous breast, colon, and prostate cells from human subjects known to have one of these types of cancer. However, prior knowledge of the patient's disease status is irrelevant to enablement. The specification teaches that an increase in the expression of SEQ ID NO: 23702 as compared to normal cells is correlated with an increased risk of having a cancerous breast, colon and prostate cell in a certain population of patients. This comparison is an appropriate methodology since it demonstrates the key discovery that the expression of SEQ ID NO: 23702 is correlated with breast, colon and prostate cancer.

State of Prior Art and Unpredictability

The fifth and sixth *Wands* factors cited by the Office are the state of the prior art and the unpredictability of the art. The Office alleges that the art does not teach detecting cancerous cells

or diagnosing cancer based on an observed increase in the expression level of SEQ ID NO: 23702 and that it is entirely unpredictable whether or not the expression level of a particular gene can be used to detect cancerous cells and diagnose cancer. In particular, the Office cites Srinivas et al. (The Lancet (2001) 2:698-704) as evidence of the difficulty of correlating sufficiently any single biomarker to a specific cancer and a study by Reinholz et al. (Clinical Cancer Research (2005) 11(10): 3722-3732) as evidence of the unpredictability and limitations of using a single marker for cancer detection. In light of the amendments to claims 7 and 30 clarifying that the methods are directed towards assessing the risk of a cell being cancerous or a patient having cancer rather than being used to detect or diagnose cancer, Applicants assert that this point is moot.

The Office also cites Russo as support for concerns regarding unpredictability of microarray data, focusing on Russo's statements that "False microarray data can be generated from degraded mRNA (page 6503)" and that "unpredictability often results from the fact that most human tissue samples used for expression analysis are a mixture of different cells (see page 6503, column 2)." Concerns regarding degraded mRNA are addressed by the thorough statistical analysis of the data as detailed in Example 105 (paragraphs [1161]-[1166]) that ensures over-expression is significant to a 95% confidence interval. The probability that degraded mRNA would generate reproducible, statistically relevant results to a 95% confidence interval is highly unlikely. Furthermore, Applicants believe the concerns raised regarding the unpredictable nature of microarray data due to heterogeneous samples are alleviated by the use of Laser Capture Microdissection (LCM) techniques in Example 105 (see, paragraph [1156]. Use of LCM is well known in the art to provide a homogenous tissue sample.

Finally, Office cites the results of Example 105 as demonstrating the highly unpredictable nature of the methods, noting that the number of patients showing a statistically significant increase in expression of SEQ ID NO:23702 varied widely between and within the cancer types tested. Applicants assert that this variability is irrelevant. An assessment of risk of cancer does not require knowing that every single patient having cancer shows a statistically significant increase in expression of SEQ ID NO: 23702. It is sufficient to know that SEQ ID NO: 23702 is significantly

over-expressed in cancerous breast, colon and prostate tissue when compared with healthy tissue in a certain percentage of patients.

The analysis described in Example 105 utilized well-established microarray technology to compare gene expression profiles of normal and healthy human tissue samples collected using LCM. The microarray data generated was subject to statistical analysis to evaluate which genes were significantly over-expressed in the cancerous tissues. The results reported in Example 105 are expressed as a percentage of the total number of subjects in which SEQ ID NO: 23702 was over expressed by at least two fold at a 95% confidence interval compared to normal cells. The presence of a correlation between the over-expression of SEQ ID NO: 23702 and cancer despite the high threshold for defining a significant relationship (greater than 2-fold difference to 95% confidence interval) demonstrates that the over-expression of SEQ ID NO: 23702 can be used to assess an increased risk of cancer.

Evaluating gene expression by comparing expression in cancerous cells to expression in normal cells is an established and valid scientific methodology. For example, the Russo reference discusses five studies that identified the expression of a single gene which displayed "significantly increased expression in malignant tissues as compared with that of normal prostate tissue" (Russo, page 6499, col. 1). Russo also discusses Martoglio et al. (2000), a study which linked gene expression profiles to ovarian cancer by comparing expression in cancerous tissues to expression in normal ovary tissues (Russo, page 6500, col. 1).

Thus, the data described in the specification illustrates that over-expression of SEC ID NO: 23702 can be an indicative biomarker and would find use in assessing the risk of a breast, colon or prostate cell being cancerous or a patient having breast, colon or prostate cancer.

Quantity of Experimentation

The seventh *Wands* factor cited by the examiner is the quantity of experimentation necessary. The Office alleges that the quantity of experimentation required to reliably demonstrate

detection or diagnosis of even one type of cancer based on the over-expression of SEQ ID NO: 23702 would be immense.

As discussed above, claim 7 has been amended to recite that the methods are directed to assessing the risk of a human breast, colon or prostate cell being cancerous by detecting over-expression of SEQ ID NO: 23702 rather than detecting and diagnosing cancer by detecting over-expression of SEQ ID NO: 23702. Claim 7 has also been amended to remove the "full complement" and "complements" language, which further limits the quantity of experimentation required. Claim 30 has been similarly amended to reflect that the methods are directed to assessing the risk of a human patient having breast, colon or prostate cancer based on over-expression of SEQ ID NO: 23702. Again, removal of the "full complement" and "complements" language further limits the quantity of experimentation required.

In light of the currently amended claims, Applicants believe the quantity of experimentation is not undue. With respect to undue experimentation, the MPEP states that, "The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm"n 1983), *aff'd. sub nom., Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985). See also *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404. The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976)."

Where the art typically engages in a complex, but routine degree of experimentation, having to do so is not the undue experimentation proscribed by 35 U.S.C. 112, first paragraph, under the reasoning of *In re Wands*. Even assuming that performing experiments as described in the references cited by the Office to confirm the correlation reported by Applicants between increased expression of SEQ ID NO: 23702 and an increased risk of having breast, colon, or prostate cancer would be "complex," Applicants submit that this kind of experimentation is routine in the art, and therefore, is not undue experimentation.

Level of Skill in Art

The eighth *Wands* factor cited by the Office is the relative skill of those in the art. The Office asserts that the level of skill in the art is deemed to be high. Applicants agree, the validation of the identified correlation between gene overexpression and cancer and the detection of nucleic acid expression levels are all routine for those of skill in the art.

Conclusion

Thus, in light of the amendments to the claims and the fact that most if not all of the cited *In re Wands* factors now weigh in favor of Applicants, it is respectfully submitted that a person skilled in the art would be able to assess the risk of a breast, colon, or prostate cell being cancerous or a patient having breast, colon or prostate cancer based on the over-expression of SEQ ID NO: 23702 using the teachings of the present application without undue experimentation. Applicants thus believe that the presently pending and amended claims are enabled under 35 U.S.C. 112, first paragraph, and request withdrawal of the rejection.

IV. Rejection under 35 U.S.C. 112, indefiniteness, second paragraph

Claim 13 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. The Office has alleged that there is insufficient antecedent basis for the term "said sample" in claim 13. As suggested by the Examiner, claim 13 has been amended to recite "said test sample". Applicants therefore request that the rejection of claim 13 under 35 USC 112 be withdrawn.

V. Conclusion

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is

determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No. **03-1952** referencing docket no. **223002106600**. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

In addition, please direct all further communications in this application to:

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